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EXAMINER	
PAPPU, SITA S	

ART UNIT	PAPER NUMBER
1632	7

DATE MAILED: 11/27/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/778,516	LO ET AL.	
	Examiner	Art Unit	
	Sita S Pappu	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-14 are pending in the instant application. This paper contains an examination of the claims 1-14 on their merits.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), in paper number 5, which papers have been placed of record in the file.

Drawings

This application has been filed with informal drawings which are acceptable for examination purposes only. The drawings are objected to because the margins of Figures 5A-6G are not accepatable. Figures 7A and 7B are of poor quality. Correction is required. See attached PTO-948.

Claim Objections

Claims 9, 11 objected to because of the following informalities: the claims refer to "ATCC Accession No." ATCC is a trademark and thus cannot be used. It is suggested to spell it out as American type Culture Collection. Appropriate correction is required.

Double Patenting

Applicant is advised that should claim 7 be found allowable, claim 8 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing

one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 7 and 8 are drawn to a Lac shuttle vector comprising the nucleotide sequence set forth in Seq ID No: 1 and 2 respectively. Our sequence processor aligned the sequences Seq ID 1 and 2 and found that they are both identical in sequence. Thus claims 7 and 8 have identical scope.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, and 11 are rejected under 35 U.S.C. 112, first paragraph, because the claims 9 and 11 refer to biological deposits to satisfy the "how to make" requirement, but fail to specify if they were made under the terms of the Budapest Treaty. If the deposits are made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific plasmids and the bacterial strain have been deposited under the Budapest Treaty and that the plasmids and the bacterial strain will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and,

(d) a test of the viability of the biological material was performed at the time of deposit (see 37 CFR 1.807); and,

(e) the deposit will be replaced if it should ever become inviable.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a Lac shuttle vector comprising an *E.coli* replication origin sequence, an eukaryotic gene expression cassette comprising a cytomegalovirus promoter, a multiple cloning site and a transcriptional terminator sequence from bovine growth hormone along with a lactic acid bacteria plasmid sequence comprising a plus origin of replication, and nucleic acid sequence that encodes a protein which regulates the lactic acid bacteria plasmid replication, and a β-

galactosidase gene under the control of erythromycin resistance gene promoter as a marker gene that is not an antibiotic resistance gene, does not reasonably provide enablement for any marker gene that is not an antibiotic resistance gene under the control of any type of promoter. Further, the specification does not provide enablement for any eukaryotic expression cassette wherein any heterologous gene can be inserted into the multiple cloning site. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

In the instant case, claim 1 is drawn to a Lac shuttle vector (a) with an E. coli replication origin sequence, (b) an eukaryotic gene expression cassette with a promoter sequence, a multiple cloning site and a transcriptional terminator sequence, wherein a heterologous gene can be inserted, (c) a lactic acid bacteria plasmid sequence with an origin of replication, and a nucleic acid sequence encoding a protein which relates to the

lactic acid bacteria plasmid sequence, (d) and a non-antibiotic resistance selection gene and the promoter sequence thereof. The specification teaches only a a Lac shuttle vector comprising an *E.coli* replication origin sequence, an eukaryotic gene expression cassette comprising a cytomegalovirus promoter, a multiple cloning site and a transcriptional terminator sequence from bovine growth hormone along with a lactic acid bacteria plasmid sequence comprising a plus origin of replication, and nucleic acid sequence that encodes a protein which regulates the lactic acid bacteria plasmid replication, and a β-galactosidase gene under the control of erythromycin resistance gene promoter as a marker gene that is not an antibiotic resistance gene. The specification does not teach how to make and use the invention with any and all heterologous genes, and with any and all non-antibiotic resistance genes as marker genes under the control of any and all promoters as claimed in the claims. The breadth and scope of claim 1, thus surpasses that enabled by the specification. Even though the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the claims as specified and use the invention with any and all genes and promoters as claimed. The specification and the working examples provide sufficient guidance to practice the invention with only a Lac shuttle vector comprising an *E. coli* replication origin sequence, an eukaryotic gene expression cassette comprising a cytomegalovirus promoter, a multiple cloning site and a transcriptional terminator sequence from bovine growth hormone along with a lactic acid bacteria plasmid sequence comprising a plus origin of replication, and nucleic acid sequence that encodes a protein which regulates

the lactic acid bacteria plasmid replication, and a β-galactosidase gene under the control of erythromycin resistance gene promoter as a marker gene that is not an antibiotic resistance gene. However, neither the specification nor the working examples provide enough guidance on how to practice the invention with any and all heterologous genes, marker genes and promoters.

Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification, discloses a Lac shuttle vector comprising an *E.coli* replication origin sequence, an eukaryotic gene expression cassette comprising a cytomegalovirus promoter, a multiple cloning site and a transcriptional terminator sequence from bovine growth hormone along with a lactic acid bacteria plasmid sequence comprising a plus origin of replication, and nucleic acid sequence that encodes a protein which regulates the lactic acid bacteria plasmid replication, and a β-galactosidase gene under the control of erythromycin resistance gene promoter as a marker gene that is not an antibiotic resistance gene.

The specification discloses that the purpose of constructing the Lac vector is to use it as DNA vaccine carrier (see specification, page 2, paragraph 2; page 3, paragraph 4; page 10, paragraph 2) by inserting antigens to pathogens and cancer in the eukaryotic expression cassette of the said vector which, when administered to

organisms, is expected to generate a therapeutic or protective immune response to a particular antigen and to prevent or treat disease in organisms.

The specification does not provide an enabling disclosure for the treatment or prevention of any and all diseases by administering the said Lac vector. In particular, the specification fails to provide sufficient guidance as to the level and character of immune responses required to achieve a therapeutic or prophylactic effect on any and all diseases. At the time of filing the art recognized that while many immunization strategies using specific antigens were capable of generating an immune response against the particular antigen, few were capable of generating a protective or therapeutically effective immune response against infections or diseases associated with the immunizing antigen.

At the time of filing, the art teaches that the strength and character of an immune response to a particular antigen or epitope significantly affects the ability of the host to successfully protect against or ameliorate disease or infection. For example, Yasutomi et al. teaches that immunization of rhesus monkeys with a live viral vector which encodes the SIV gag protein generate a non-protective CTL response, but fails to generate a humoral immune response despite the presence of MHC class II and antibody binding epitopes in the gag protein (Yasutomi et al. (1995) J. Virol., Vol. 69 (4), page 2279, abstract). In addition, Yasutomi et al. teaches that while boosting vaccinated animals with a gag peptide/liposome complex significantly increases the anti-gag CTL response, it still did not provide increased protection against SIV challenge (Yasutomi et al., *supra*, abstract). In the case of pseudorabies virus, Monteil et al. discloses that the

immunization of naive one-day-old piglets with a plasmid DNA encoding the gene for the gD glycoprotein induces antibodies which do not protect the piglets from PRV challenge (Monteil et al. (1996) Veterinary Research, Vol. 27 (4-5), page 443, abstract).

Another complicating factor in generating a therapeutic immune response involves the stimulation of a Th1 versus a Th2 response. Certain parasites, such as Leishmania or Nipponstrongulus, and autoimmune diseases such as EAE (experimental allergic encephalomyelitis) and diabetes are adversely affected by the presence of activated antigen specific Th1 versus Th2 T cells. Further, in a review of genetic immunization, Ertl and Zhiang emphasize the critical role of the antigen by stating that, " although any antigens can be delivered by genetic immunization, some proteins upon expression by plasmid vectors remain immunologically silent. The principles that govern success versus failure of genetic immunization with regard to each individual protein remain to be elucidated" (Ertl et al. (1996), Viral Immunology, Vol. 9 (1), page 2, lines 32-35).

The specification does not provide sufficient guidance as to the level of antigen specific antibody and or CTL response required to protect or treat such disparate diseases as cancer and HIV, or as to the generation of antigen specific immune responses using routes of administration disclosed in the specification, for the vector to be useful as an effective DNA vaccine carrier. Further, at the time of filing, vaccination against diseases such as HIV and cancer were considered highly unpredictable. Fox in a review of the "First National Conference on Human Retroviruses and Related Infections" summarizes the conference's central theme as, "no therapy has emerged as

a sure winner in the campaign against HIV, not a preventive vaccine nor a therapeutic vaccine nor any of the immune-system-boosting treatments" (Fox (1994) Bio/Technology, 12, 128). In regards to the treatment of cancer using cytokines, Ross et al. relates that while, " there is only 1 patient to date who might be considered to have had a significant systemic clinical response " to cytokine therapy of a melanoma, "success in a single patient does not imply the general utility of this approach" (Ross et al. (1996) Human Gene Therapy, Vol. 7, page 1786, column 1, paragraph 4). Orkin et al. concurs, stating in regards to cytokine-mediated cancer therapy that, " although several of these strategies show promise in mouse models, none has demonstrated efficacy in humans", and that, " [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol.." (Orkin et al. (1995) page 1, paragraph 3, page 6, paragraph 6).

Therefore, based on the lack of guidance in the specification as to the level and character of immune responses required to achieve a therapeutic or prophylactic effect on any and all diseases using the instant methodology, the art recognized unpredictability of protecting against or treating any and all diseases, particularly HIV and cancer, using gene therapy, and the breadth of the claims, it would have required undue experimentation for the skilled artisan at the time of filing to practice the full scope of the instant invention as claimed in claim 13.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claim 1, 4, 5, 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention.

Claim 1, step (b) recites "wherein a heterologous gene is inserted into said multiple cloning site" but fails to point out what the term heterologous refers to. It is unclear whether it is heterologous in relation to *E. coli*, *Lactobacillus* or eukaryotic genomes. Similarly claim 12 recites "a kit for the expression of a heterologous gene". Applicants are advised to clearly point out and specifically claim their invention.

Claim 1, step (d), and claim 5, recite "a non-antibiotic resistance selection gene". It is suggested that changing the claim language to "a marker gene that is not antibiotic resistance gene" would make the meaning of the claim1, step (d) more clear.

Claim 4, recites "Rep A protein containing 317 amino acids". The term containing is read as open claim language. It is suggested that the use of the word "consisting essentially of" in place of "containing" would make the meaning more clear. Further, replacing the term "relates to", with another term such as "regulates" or "involved in" is suggested.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: Claim 1, step (c),

recites "a nucleic acid sequence encoding for a protein which relates to the lactic acid bacteria plasmid replication". According to the accepted usage of the English language, a nucleic acid sequence can code for a protein or alternatively it can encode a protein. Usage of the terms "encoding for" renders the claim indefinite. Therefore, it is suggested that the applicant change the wording of the claim1, step (c) to bring it into conformity with accepted usage of the language. Further, claim 1, step (c), recites "a protein which relates to the ----plasmid replication", wherein the meaning of the word "relates to" is unclear since it does not explain how the protein relates to the plasmid replication. It is suggested that the use of the term "regulates" or "involved in" would make the meaning and the relationship of the protein with plasmid replication more clear.

Regarding claim 11, the phrase "Lac$^-$ mutant" in parentheses after Ana-1, renders the claim indefinite because it is unclear whether the limitation(s) that is in parentheses, following the phrase Ana-1 is merely descriptive of Ana-1 or a further limitation of the claimed invention. Similarly, the phrase "subsp. *casei* " within parentheses renders the claim indefinite. See MPEP § 2173.05(d). It is suggested to remove the parentheses and amend the claim to read "wherein the host cell is the Lac- mutant of *Lactobacillus casei*, subsp. *casei*, which is designated Ana-1".

Claim 13 is indefinite in its recitation of "a DNA vaccine carrier comprising the Lac shuttle vector" because a carrier plus vector is a composition, not a carrier. The claim language is confusing because it is unclear whether the claim is directed to the carrier itself or a vaccine composition.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: there is no conclusory statement at the end of claim 14 and it renders the method of claim 14 incomplete since it does not recite the selection step. It is suggested that addition of a phrase such as "thereby selecting a host cell containing Lac shuttle vector of claim 1" would complete the method steps.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bringel et al. (1989; Plasmid vol 22 (3), pages 193-202), in view of Hemme et al. (1994: Letters in Applied Microbiology 19:345-348) and Dietrich et al. (1998; Nature Biotechnology vol 16 :181-185).

Specification discloses that the novelty of the instant invention lies in that the Lac vector of the instant invention uses the β-galactosidase gene from *Lactobacillus delbrueckii* as a marker gene that is non-antibiotic resistant gene. See specification, page 1, lines 6-9; page 2, lines 11-15).

Bringel et al. (1989) teach a 2.1 kb plasmid, pLP1, from *Lactobacillus plantarum* that contains the replication protein and its use in constructing shuttle vectors (see abstract, page 193).

Bringel et al. (1989) do not teach the use of β-galactosidase gene from Lactobacillus delbrueckii as a marker gene that is non-antibiotic resistant gene.

Hemme et al. (1994) teach the use of β-galactosidase gene on a Lactobacillus casei plasmid and its ability to rescue Lac- mutants (page 345, see abstract).

Dietrich et al. (1998) teach the delivery of antigen encoding plasmid DNA in a eukaryotic expression cassette in a shuttle vector by Listeria monocytogenes.

Dietrich et al. (1988) do not teach their work in the context of Lactobacillus palntarum plasmid DNA.

Motivation to combine the teachings, with a reasonable expectation of success, was provided by the state of the art at the time of filing and the need to address the safety issues in DNA vaccination (see Dietrich et al. 1998. page 184, right column, 2nd paragraph).

Therefore, it would have been obvious to a person with ordinary skill in the art to combine the teachings of Bringel et al.(1989), Hemme et al. (1994) and Dietrich et al. (1998) and arrive at the Lac shuttle vector of the instant invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (9:00 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached on (703) 305-6608. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-2758.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER

S. Pappu
November 16, 2001